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Larger Thigh and Hip Circumferences Are Associated with Better Glucose Tolerance: The Hoorn Study

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Abstract

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Objective: A higher waist-to-hip ratio, which can be due to a higher waist circumference, a lower hip circumference, or both, is associated with higher glucose levels and incident diabetes. A lower hip circumference could reflect either lower fat mass or lower muscle mass. Muscle mass might be better reflected by thigh circumference. The aim of this study was to investigate the contributions of thigh and hip circumferences, independent of waist circumference, to measures of glucose metabolism.

Research Methods and Procedures: For this cross-sectional study we used baseline data from the Hoorn Study, a population-based cohort study of glucose tolerance among 2484 men and women aged 50 to 75. Glucose tolerance was assessed by a 75-g oral glucose tolerance test; hemoglobin A_{1c} and fasting insulin were also measured. Anthropometric measurements included body mass index (BMI) and waist, hip, and thigh circumferences.

Results: Stratified analyses and multiple linear regression showed that after adjustment for age, BMI, and waist circumference, thigh circumference was negatively associated with markers of glucose metabolism in women, but not in men. Standardized β values in women were -0.164 for fasting, -0.206 for post-load glucose, -0.190 for hemoglobin A_{1c} (all $p < 0.001$), and -0.065 for natural log insulin levels ($p = 0.061$). Hip circumference was negatively associated with markers of glucose metabolism in both sexes (standardized betas ranging from -0.093 to -0.296, $p < 0.05$) except for insulin in men. Waist circumference was positively associated with glucose metabolism.

Discussion: Thigh circumference in women and hip circumference in both sexes are negatively associated with markers of glucose metabolism independently of the waist circumference, BMI, and age. Both fat and muscle tissues may contribute to these associations.

Key words: fat distribution, diabetes mellitus, waist-to-hip ratio, body composition, glucose intolerance

Introduction

It is firmly established that obesity is associated with a higher prevalence of type 2 diabetes. The accumulation of visceral fat is particularly assumed to play an important role in the etiology of the disease, notably by the overexposure of the liver to free fatty acids, which results in insulin resistance and hyperinsulinemia (1,2).

Waist circumference and waist-to-hip ratio (WHR)[1] are widely used as indicators of abdominal obesity in population studies. The majority of current studies agree that waist circumference is probably a better indicator of visceral fat than is WHR. Indeed, several studies found waist circumference to be a better marker of visceral fat and to correlate more strongly with cardiovascular risk factors than WHR (3,4). However, the WHR is a robust risk factor in many

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[1] Nonstandard abbreviations: WHR, waist-to-hip ratio; WTR, waist-to-thigh ratio; HbA_{1c}, hemoglobin A_{1c}; BMI, body mass index; Ln, natural log; GH, growth hormone.

population studies, and other studies found WHR or waist-to-thigh ratio (WTR) to be a better predictor for type 2 diabetes than waist circumference alone (5). Moreover, a larger hip circumference has been associated with a lower risk of type 2 diabetes, independently of waist circumference (6). The underlying mechanism for this phenomenon is not yet clear, but may be related to the amount of muscle mass, the amount of fat mass, or both.

Thigh circumference might be a better indicator for leg-muscle mass than hip circumference because it might be less influenced by bone (pelvic width) and gluteal fat. In this study, we consider the independent contributions of thigh or hip circumferences to several measures of glucose metabolism after adjustment for waist circumference. Because lifestyle factors are known to influence fat distribution and glucose metabolism (7,8), we studied potential confounding by smoking, alcohol intake, and physical activity. We used data from the Hoorn Study, a cohort study of glucose tolerance in 2484 subjects.

Research Methods and Procedures

Subjects

The Hoorn Study is a population-based cohort study of glucose tolerance among 2484 white men and women aged 50 to 75, which started in 1989 and has been described in detail previously (9). For the present study, baseline measurements were used. Subjects who were already known to have diabetes were excluded from analyses ($n = 90$), and 14 subjects had missing data for glucose measures and/or anthropometry; therefore, analyses were performed in 2380 subjects (1099 men and 1281 women). Informed consent was obtained from all participants, and ethical approval for the study was obtained from the local ethics committee.

Measurements

Fasting glucose and post-load glucose levels after a 75-g oral glucose tolerance test were measured as previously described (9). Subjects were classified according to the 1999 World Health Organization criteria (10). Glycated hemoglobin A_{1c} (HbA_{1c}), used as a long-term indicator of glucose levels, and fasting-specific insulin level were measured as previously described (11). Fasting insulin levels can be used as an estimate of insulin insensitivity (12).

Weight and height were measured in barefoot subjects wearing light clothes only, and body mass index (BMI) was calculated as weight divided by height squared (kilograms per meters squared). Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest, and the hip circumference at the widest level over the trochanters. Thigh circumference was measured directly below the gluteal fold at the left leg. The mean value of two measurements was used in the analyses. WHR was calculated as waist circumference divided by hip circumference and WTR as waist circumference divided by thigh circumference.

Information on lifestyle factors was obtained by questionnaire. Smoking was expressed in cigarette years for smokers or former smokers. Alcohol intake was categorized in four groups: nondrinkers, up to 10 g/d, 10 to 30 g/d, and >30 g/d. Physical activity was expressed as hours per day. The activities included sports, bicycling, gardening, walking, doing odd jobs, and housekeeping.

Statistical Methods

All statistical analyses were performed separately for men and women because of the known differences in fat distribution between sexes. Baseline characteristics are reported according to glucose tolerance status. Differences between men and women were examined by Student's *t* test. Because the distribution of insulin levels was skewed, geometric means are presented.

To study the contribution of thigh circumference to glucose metabolism independently of waist circumference, sex-specific tertiles of waist circumference and of thigh circumference were created. We divided the population of each sex into nine groups by creating a 3×3 table according to these tertiles, and calculated the unadjusted means of age, BMI, and glucose metabolism variables (fasting and post-load glucose, HbA_{1c}, and fasting insulin) in each group. Additionally, we calculated means of glucose variables adjusted for age and overall obesity (BMI). These analyses were repeated using hip circumference instead of thigh circumference. To test for trend, the categorical variable of thigh or hip tertiles was entered in a linear regression model as a continuous variable with the glucose-metabolism variable as dependent variable. Insulin levels were natural log (Ln)-transformed because of their skewed distribution.

We also studied the independent contribution of thigh and waist circumferences to glucose metabolism in a multiple linear regression model using thigh and waist circumferences as continuous variables, with adjustment for age and BMI. To make regression coefficients more comparable, we report standardized β values. A standardized β of 0.1 indicates that if the independent variable changes one SD, the dependent variable changes 0.1 SD. In an additional model, further adjustments were made for lifestyle factors (smoking, alcohol intake, and physical activity). We repeated these analyses using hip circumference instead of thigh circumference. Multicolinearity in these regression models was studied by examining the tolerance, which is a statistic used to determine how much the independent variables are linearly related to one another. It is calculated as $1 - R^2$ for an independent variable when it is predicted by the other independent variables already included in the analysis. The stability of the regression model was considered to be disturbed by multicolinearity if tolerance was <0.1. All analyses were performed using the SPSS/PC statistical program (version 10.1 for Windows; SPSS, Inc., Chicago, IL).

Table 1. Population characteristics according to sex and glucose tolerance status, expressed as mean (SD)

	Men				Women			
	Total	**NGT***	**IGT and/or IFG***	**DM***	**Total**	**NGT***	**IGT and/or IFG***	**DM***
n	1099	807	209	81	1281	977	213	83
Age (years)	61.2 (7.3)†	60.7 (7.2)	62.3 (7.2)	63.7 (7.1)‡	61.8 (7.4)	60.9 (7.2)	64.7 (7.2)	65.4 (7.0)‡
Fasting glucose (mM)	5.68 (1.08)†	5.34 (0.40)	6.13 (0.45)	7.97 (2.62)‡	5.51 (1.09)	5.20 (0.42)	5.96 (0.52)	7.98 (2.80)‡
Postload glucose (mM)	5.92 (2.93)†	4.95 (1.29)	7.07 (2.00)	12.65 (5.63)‡	6.19 (2.89)	5.23 (1.17)	7.82 (1.72)	13.47 (5.81)‡
HbA_{1c} (%)*	5.43 (0.69)	5.33 (0.47)	5.46 (0.52)	6.41 (1.56)‡	5.40 (0.68)	5.28 (0.47)	5.57 (0.46)	6.46 (1.64)‡
Fasting insulin (pM)§	79.22	74.21	93.16	100.04‡	77.28	73.14	87.34	108.40‡
BMI (kg/m^2)*	26.2 (2.9)†	25.7 (2.6)	27.1 (3.2)	28.3 (3.2)‡	26.7 (3.9)	26.3 (3.7)	28.0 (4.0)	28.5 (4.6)‡
Waist circumference (cm)	95.25 (9.14)†	93.74 (8.19)	98.35 (10.64)	102.23 (8.64)‡	86.82 (10.52)	85.33 (9.90)	90.98 (10.70)	94.04 (11.54)‡
Thigh circumference (cm)	56.55 (4.79)†	56.19 (4.63)	57.25 (4.74)	58.27 (5.91)‡	59.36 (5.80)	59.50 (5.88)	59.08 (5.45)	58.55 (5.66)
Hip circumference (cm)	100.26 (5.39)†	99.79 (5.03)	101.11 (6.35)	102.91 (5.18)‡	102.73 (7.49)	102.42 (7.34)	103.61 (7.77)	104.27 (8.27)‡
WHR*	0.95 (0.06)†	0.94 (0.06)	0.97 (0.07)	0.99 (0.07)‡	0.84 (0.07)	0.83 (0.07)	0.88 (0.07)	0.90 (0.08)‡
WTR*	1.69 (0.15)†	1.67 (0.15)	1.72 (0.16)	1.76 (0.16)‡	1.47 (0.17)	1.44 (0.16)	1.54 (0.15)	1.61 (0.19)‡

* NGT, normal glucose tolerance; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; DM, diabetes mellitus; HbA_{1c}, glycated haemoglobin; WHR, waist-to-hip ratio; WTR, waist-to-thigh ratio.

† $p < 0.05$ comparing men and women.

‡ p trend < 0.01 comparing glucose tolerance categories.

§ Geometric mean. Glucose tolerance status could not be assessed in 10 subjects (2 men/8 women) because of missing post-load glucose level.

Results

Baseline characteristics are presented in Table 1. As expected, age, BMI, waist circumference, WHR, and WTR increased with worsening glucose tolerance status. Also, the hip and thigh circumferences were significantly positively associated; however, the associations were not strong, and the association with thigh circumference in women was not significant ($p = 0.106$) and tended to reverse. The correlation between waist and hip circumference was higher ($r = 0.73$ for men and $r = 0.71$ for women) than the correlation between waist and thigh circumference ($r = 0.48$ for men and $r = 0.43$ for women).

Stratified Analyses

Table 2 shows that a higher waist circumference was associated with older age, higher BMI, and higher glucose and insulin levels. In men with a small waist, there was a statistically significant negative association of thigh circumference with HbA_{1c} and post-load glucose levels, despite the positive association between thigh and BMI. Insulin was positively associated with thigh circumference. In women, the negative associations of thigh circumference with glucose levels and HbA_{1c} were more pronounced. Fasting insulin was positively associated with thigh circumference in women with a low waist circumference, but in women with a high waist circumference, the association inverted. The same analyses were performed using tertiles of hip circumference instead of thigh circumference to create the nine groups for each sex. Similar results were found (data not shown), but the number of subjects in the subgroups with low waist and high hip (and vice versa) was relatively small (range $n = 27$ to $n = 36$).

Figure 1 (A and B) illustrates the means of fasting glucose and post-load glucose levels, respectively, adjusted for age and BMI. In women, but not in men, there was an inverse association of thigh circumference with glucose levels. When testing for trend within tertiles of waist circumference, there was a significant negative association between thigh circumference and fasting glucose levels in women in the uppermost tertile of waist circumference ($p < 0.001$). The negative association of thigh circumference with post-load glucose levels was shown in women in all waist tertiles ($p = 0.047$, 0.080, and <0.001 for low, medium, and high waist circumference, respectively). In men, no significant association of thigh circumference with glucose measures was shown. The figures also suggest interaction (effect modification) between waist and thigh circumference in women. This indicates that in women with a large waist circumference in particular, a greater thigh circumference is associated with lower glucose levels. A similar pattern was observed for adjusted HbA_{1c} and fasting insulin levels (data not shown). When we used tertiles of hip circumference instead of thigh circumference, similar results were obtained in women. In men, the inverse association of hip circumference with fasting and post-load glucose levels (but not with HbA_{1c} or fasting insulin) was also

Table 2. Unadjusted means of age, body mass index (BMI), and glucose metabolism markers in subgroups of low, medium, and high (1 through 3) thigh and waist circumferences

		Men			Women		
		Tertiles of thigh			Tertiles of thigh		
Tertiles of waist	Cutoff points	1 ≤54.4 cm	2	3 ≥58.3 cm	1 ≤56.5 cm	2	3 ≥61.5 cm
1	*n*	194	115	61	216	142	70
≤91.0 cm	Age (years)	61.7	58.7	56.5*	61.9	58.4	57.3*
(Men)	BMI (kg/m^2)	22.7	24.8	25.2*	22.4	24.0	25.5*
≤81.7 cm	Fasting glucose†	5.38	5.45	5.42	5.23	5.19	5.17
(Women)	Post-load glucose†	5.20	5.12	4.68‡	5.66	5.47	4.99‡
	HbA_{1c} (%)	5.41	5.30	5.25*	5.34	5.20	5.13*
	Fasting insulin§	62.66	64.81	73.75*	60.33	67.09	68.87*
2	*n*	104	135	119	144	152	135
	Age (years)	63.4	61.3	58.2*	63.3	62.5	60.4*
	BMI (kg/m^2)	24.8	25.8	27.2*	24.8	26.7	27.9*
	Fasting glucose†	5.55	5.62	5.59	5.49	5.34	5.45
	Post-load glucose†	5.77	5.90	5.33	6.36	5.87	5.66*
	HbA_{1c} (%)	5.47	5.30	5.28*	5.43	5.36	5.31‡
	Fasting insulin§	78.23	74.41	80.83	77.60	72.26	74.72
3	*n*	61	125	185	65	129	228
≥99.0 cm	Age (years)	69.0	63.0	60.8*	65.5	63.6	62.8*
(Men)	BMI (kg/m^2)	26.7	27.8	30.0*	27.5	29.0	32.0*
≥90.6 cm	Fasting glucose†	5.95	6.00	6.10	6.38	6.00	5.69*
(Women)	Post-load glucose†	7.02	6.73	7.18	8.65	7.49	6.49*
	HbA_{1c} (%)	5.65	5.58	5.59	5.88	5.67	5.46*
	Fasting insulin§	94.15	93.38	103.2‡	106.61	96.87	94.16‡

* p trend < 0.05.
† mM.
‡ p trend < 0.01.
§ pM, geometric mean.

shown, although this association was significant only for post-load glucose with medium waist circumference (p trend = 0.028) (data not shown).

Multiple Linear Regression

Table 3 shows that both in men and in women, the waist circumference was strongly positively associated with all measures of the glucose metabolism (fasting and post-load glucose, HbA_{1c}, and insulin) after adjustment for age, BMI, and thigh circumference (model 1). In the same model, thigh circumference was negatively associated with markers of the glucose metabolism in women only.

We tested the potential interaction suggested by Figure 1 between thigh and waist circumference by adding an interaction term of thigh and waist to the regression model. In men, we did not find significant interaction for glucose and insulin levels. In women, we observed significant interaction of waist and thigh in the models with fasting and post-load glucose levels and fasting insulin levels (p = 0.005, 0.008, and 0.030, respectively), but not for HbA_{1c}. In an additional regression model, we also adjusted for the lifestyle factors of smoking, physical activity, and alcohol intake. These factors did not markedly change our results (data not shown). When applying the same multiple regression analyses using hip circumference instead of thigh circumference (Table 3, model 2), we found that both waist and hip contributed significantly to the glucose variables in both sexes, except for fasting insulin in men. No interaction

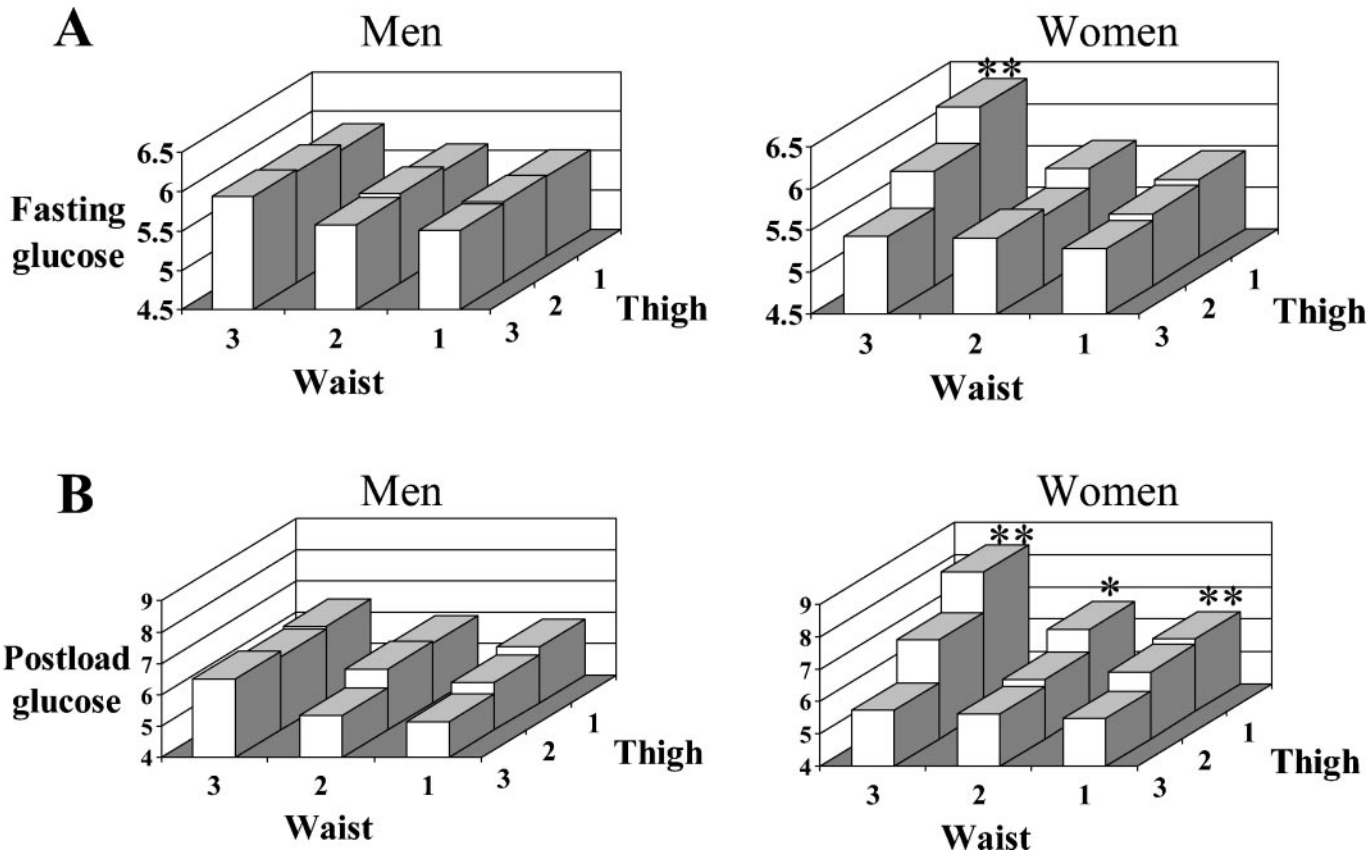

Figure 1: BMI- and age-adjusted means of fasting glucose levels (A) and post-load glucose levels (B) in subgroups of low, medium, and high (1 through 3) waist and thigh circumferences, for men and women separately. $p < 0.1$ (*) and $p < 0.05$ (**) when testing for trend within tertiles of waist circumference.

between hip and waist was observed. Additional adjustment for lifestyle factors did not substantially change these results (data not shown). In none of the regression models was the stability of estimated parameters influenced by multicolinearity.

Discussion

This study demonstrates that after adjustment for age and overall obesity (BMI), thigh circumference was strongly and negatively associated with markers of glucose metabolism in women, but not in men. Hip circumference was negatively associated with markers of glucose metabolism in both sexes. These associations were independent of waist circumference, which was positively associated with these markers. Only in women, we observed a significant interaction between thigh and waist circumference, indicating that women with a combination of large waist and small thigh circumferences seem to have worse glucose levels than women with smaller waists or larger thighs. Adjustment for lifestyle factors did not change the associations.

These results are in accordance with previously published data concerning the specific contribution of hip circumference to disease risk (6,13,14). Seidell et al. recently reported that hip circumference was independently and negatively associated with several cardiovascular risk factors, including fasting insulin and fasting glucose, in the Quebec Family Study (15). A limitation of the latter study was the inclusion of younger subjects (age range 18 to 84 years), which might have weakened the associations, because disturbances in glucose metabolism usually appear at an older age. In addition, only fasting glucose and insulin were measured. Our study extends these findings by also including post-load glucose and HbA_{1c} measurements. Furthermore, to our knowledge, this is the first study to include both thigh and hip circumference to compare their independent influence on glucose metabolism.

The increased risk of unfavorable glucose levels in subjects with higher WHR or WTR is generally thought to be attributable to increased visceral fat mass (1,2). Indeed, we confirm a strong positive association of waist circumference with markers of glucose metabolism. A higher WHR or WTR, however, may also result from a lower hip or thigh circumference. Indeed, a higher WHR was found to be associated with a decreased muscle mass in the legs and

Table 3. Independent contributions of waist and thigh circumferences (model 1) and waist and hip circumferences (model 2) to glucose metabolism markers, in linear regression models adjusted for age and body mass index (BMI)

Model 1*	Waist circumference†	*p*	Thigh circumference‡	*p*
Fasting glucose				
Men	0.179	0.001	−0.019	0.651
Women	0.280	0.000	−0.164	0.000
Post-load glucose				
Men	0.154	0.003	−0.057	0.163
Women	0.249	0.000	−0.206	0.000
HbA_{1c}				
Men	0.132	0.013	−0.053	0.208
Women	0.277	0.000	−0.190	0.000
Ln-insulin				
Men	0.294	0.000	0.018	0.637
Women	0.280	0.000	−0.065	0.061
Model 2*	**Waist circumference†**	***p***	**Hip circumference†**	***p***
Fasting glucose				
Men	0.221	0.000	−0.103	0.029
Women	0.351	0.000	−0.222	0.000
Post-load glucose				
Men	0.243	0.000	−0.212	0.000
Women	0.339	0.000	−0.296	0.000
HbA_{1c}				
Men	0.175	0.002	−0.097	0.043
Women	0.348	0.000	−0.183	0.000
Ln-insulin				
Men	0.283	0.000	0.023	0.602
Women	0.308	0.000	−0.093	0.040

* Model 1 includes waist circumference, thigh circumference, BMI, and age as independent variables; model 2 includes waist circumference, hip circumference, BMI, and age as independent variables.
† Standardized betas.

gluteal region (16). Therefore, it has been speculated that the contribution of larger hip circumference to lower glucose levels may be due to higher muscle mass (6). Skeletal muscle is the main target of insulin, as well as one of the sites of insulin resistance. Low muscle mass has been associated with insulin resistance. Chowdhury et al. showed that higher glucose levels in Indian, compared with Swedish, men of the same age and BMI were not due to differences in visceral fat, but to their lower leg muscle mass (17). Also, a high WHR has been associated with a higher proportion of type IIb muscle fibers and lower capillary density at the thigh, which may be associated with decreased glucose transport and reduced insulin sensitivity (18,19).

Larger thigh and hip circumferences could also reflect increased femoral and gluteal subcutaneous fat, respectively. Particularly in women, these depots have relatively high lipoprotein lipase activity and relatively low rate of basal and stimulated lipolysis (20). These depots may protect the liver and muscle from high exposure to free fatty acids, through uptake and storage. The regional differences in adipocyte metabolism are more pronounced in women than in men. This could possibly explain why we did find a negative association between thigh circumference and glucose levels in women, but not in men. In contrast, hip circumference was associated with glucose metabolism in both sexes. Interpretation of the hip circumference, how-

ever, may be different between men and women. It is plausible that variation in hip circumference in women is explained mostly by variation in gluteal fat mass and pelvic width, whereas in men, muscle mass might be the main determinant.

Underlying hormonal factors may influence waist, thigh, and hip circumferences, as well as insulin resistance. Disturbances in glucocorticoid metabolism, growth hormone (GH) metabolism, and sex hormone balance have all been shown to be associated with alterations in fat distribution, as well as deterioration in insulin resistance and glucose metabolism (21). Cushing's syndrome, which is characterized by high cortisol levels, leads to increased visceral fat and decreased muscle mass in the legs and to hyperglycemia (22). Striking similarities exist between the metabolic syndrome and untreated GH deficiency (23). Low-dose GH treatment combined with dietary restriction resulted in a decrease of fat and in an increase of muscle mass with a consequent improvement of the insulin resistance (24). Finally, sex steroids have also been shown to influence both fat distribution and insulin sensitivity (21,25). For instance, high androgen levels in women and low testosterone levels in men are associated with measures of fat distribution and insulin resistance (26–29). Estrogens stimulate accumulation of subcutaneous fat at the gluteal and femoral depots in women. The mechanisms by which endocrine disturbances lead to abdominal fat distribution and decreased insulin sensitivity are not completely clear. It has been suggested that the effect of these hormones on lipoprotein lipase activity in adipose tissue may be involved (13,22,25). Adipose tissue is an endocrine organ secreting many peptides. These peptides include leptin, resistin, adiponectin, angiotensinogen, interleukin-6, tumor necrosis factor-α, adipsin, and plasminogen activator inhibitor-1 (30). Regional differences in secretion of these peptides could also be an alternative or additional explanation for the relationships between circumferences and glucose levels that we found.

Another underlying factor that possibly contributes to a disturbed glucose metabolism and an abdominal fat distribution could be intrauterine growth retardation (low birth weight). A low birth weight is associated with increased adult WHR and insulin resistance (31). Studies examining the fetal origins hypothesis suggest that small birth size may be a marker of fetal adaptations that program future vulnerability to adult disease (32). For type 2 diabetes, this may result from an altered development and insulin-secreting capacity of the endocrine pancreas, or by altered insulin sensitivity of target tissues (33).

A limitation of the present study was its cross-sectional nature. Thus, the possibility that a smaller hip circumference is not a risk factor for high glucose levels, but rather the consequence of the same underlying factor, cannot be excluded. Recently, however, Lissner showed that smaller hip circumferences predicted the incidence of self-reported diabetes in women in a prospective study (34).

In conclusion, thigh circumference in women and hip circumference in both sexes are negatively associated with markers of glucose metabolism, independently of waist circumference, BMI, and age. Further investigation, particularly prospective research, is needed to elucidate the underlying mechanisms that lead to the negative association of thigh and hip circumferences with glucose levels as observed in this study.

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